

AMENDMENTS TO THE CLAIMS

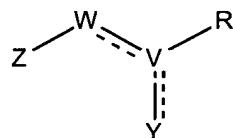
Please amend claims 26, 58, 59, 60, 61, 62, 64, 67, 69, 75, 76, 77, 78, 79 and 80 and please cancel without prejudice or disclaimer claims 2-25, 27-52, and 54.

The following listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Original) A method of inhibiting dynamin-dependent endocytosis in cells, the method comprising treating the cells with an effective amount of a compound of formula I, or a physiologically acceptable salt thereof, wherein

M-Sp-M' Formula I

M and M' are each independently a moiety of formula II and are the same or different, and Sp is a spacer;



Formula II

V is C or CH;

W is CH or a linker group; and

Y is hydrogen, cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy, sulfur, or an unsubstituted C₁-C₃ group or C₁-C₃ group substituted with at least one group independently selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur; or

W, V and Y form a 5 or 6 membered substituted or unsubstituted heterocyclic or carbocyclic ring fused with Z, wherein the heterocyclic ring includes from 1 to 3 heteroatoms selected from O, N and S, and the heterocyclic or carbocyclic ring, when

substituted, has at least one substituent selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy, sulfur, or an unsubstituted C₁-C₃ group or C₁-C₃ group substituted with at least one group independently selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur; and

R is CH₂R', CXR' or CHX'R';

X is O or S;

X' is cyano, nitro, amino, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy, or an unsubstituted C₁-C₃ group or C₁-C₃ group substituted with at least one group independently selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur;

R' is NH, O or S bonded to the spacer; and

Z is selected from:

(a) an unsubstituted heterocyclic group consisting of one or two rings independently having 5 or 6 ring members including up to 3 heteroatoms selected from O, N and S;

(b) an unsubstituted carbocyclic group consisting of one or two rings independently having 5 or 6 ring members;

(c) a heterocyclic group consisting of one or two rings independently having 5 or 6 ring members including up to 3 heteroatoms selected from O, N and S wherein the heterocyclic group has one or more substituents independently selected from:

(i) nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, C₁-C₂ alkoxy and C₁-C₂ acyl ; and

(ii) a C₁-C₂ alkyl or C₁-C₂ alkenyl group with at least one substituent selected from nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, C₁-C₂ alkoxy and C₁-C₂ acyl ; and

(d) a carbocyclic group consisting of one or two rings independently having 5 or 6 ring members, and at least two substituents when W is CH or a linker group or W, V and Y form an unsubstituted carbocyclic group, or at least one substituent when W, V and Y form a heterocyclic group, independently selected from:

(i) nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, C₁-C₂ alkoxy and C₁-C₂ acyl ; and

(ii) a C₁-C₂ alkyl or C₁-C₂ alkenyl group with at least one substituent selected from nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, C₁-C₂ alkoxy and C₁-C₂ acyl ;

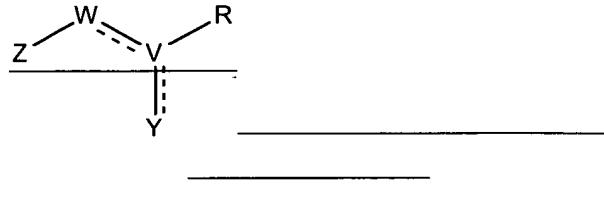
wherein when Z of one of M or M' is selected from (b), Z of the other of M or M' is selected from (a), (c) or (d).

Claims 2-25 (Cancelled).

26. (Currently Amended) A method of prophylaxis or therapeutic treatment of a disease or condition in a mammal mediated by dynamin-dependent endocytosis, the method comprising administering to the mammal an effective amount of a compound of Formula I according to claim 1, or a physiologically acceptable salt, or prodrug thereof, ~~wherein:~~

M-Sp-M' Formula I

~~M and M' are each independently a moiety of formula II and are the same or different, and Sp is a spacer;~~



Formula II

~~V is C or CH;~~

~~W is CH or a linker group; and~~

~~Y is hydrogen, cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy, sulfur, or an unsubstituted C₁-C₃ group or C₄-C₃ group substituted with at~~

~~least one group independently selected from cyano, nitro, NH, amino, exo, halo, hydroxy, sulphydryl, carboxy, thiocarboxy and sulfur; or~~

~~W, V and Y form a 5 or 6 membered substituted or unsubstituted heterocyclic or carbocyclic ring fused with Z, wherein the heterocyclic ring includes from 1 to 3 heteroatoms selected from O, N and S, and the heterocyclic or carbocyclic ring, when substituted, has at least one substituent selected from cyano, nitro, NH, amino, exo, halo, hydroxy, sulphydryl, carboxy, thiocarboxy, sulfur, or an unsubstituted C₁-C₃ group or C₁-C₃ group substituted with at least one group independently selected from cyano, nitro, NH, amino, exo, halo, hydroxy, sulphydryl, carboxy, thiocarboxy and sulfur; and~~

~~R is CH₂R', CXR' or CHX'R';~~

~~X is O or S;~~

~~X' is cyano, nitro, amino, halo, hydroxy, sulphydryl, carboxy, thiocarboxy, or an unsubstituted C₁-C₃ group or C₁-C₃ group substituted with at least one group independently selected from cyano, nitro, NH, amino, exo, halo, hydroxy, sulphydryl, carboxy, thiocarboxy and sulfur;~~

~~R' is NH, O or S bonded to the spacer; and~~

~~Z is selected from:~~

~~(a) an unsubstituted heterocyclic group consisting of one or two rings independently having 5 or 6 ring members including up to 3 heteroatoms selected from O, N and S;~~

~~(b) an unsubstituted carbocyclic group consisting of one or two rings independently having 5 or 6 ring members;~~

~~(c) a heterocyclic group consisting of one or two rings independently having 5 or 6 ring members including up to 3 heteroatoms selected from O, N and S wherein the heterocyclic group has one or more substituents independently selected from:~~

~~(i) nitro, NH, amino, cyano, halo, hydroxy, carboxy, exo, sulfur, sulphydryl, C₁-C₂ alkoxy and C₁-C₂ acyl; and~~

~~(ii) a C₁-C₂ alkyl or C₁-C₂ alkenyl group with at least one substituent selected from nitro, NH, amino, cyano, halo, hydroxy, carboxy, exo, sulfur, sulphydryl, C₁-C₂ alkoxy and C₁-C₂ acyl; and~~

(d) ~~a carbocyclic group consisting of one or two rings independently having 5 or 6 ring members, and at least two substituents when W is CH or a linker group or W, V and Y form an unsubstituted carbocyclic group, or at least one substituent when W, V and Y form a heterocyclic group, independently selected from:~~

(i) ~~nitro, NH, amino, cyano, halo, hydroxy, carboxy, o xo, sulfur, sulfhydryl, C₁-C₂-alkoxy and C₁-C₂-acyl; and~~

(ii) ~~a C₁-C₂-alkyl or C₁-C₂-alkenyl group with at least one substituent selected from nitro, NH, amino, cyano, halo, hydroxy, carboxy, o xo, sulfur, sulfhydryl, C₁-C₂-alkoxy and C₁-C₂-acyl;~~

~~wherein when Z of one of M or M' is selected from (b), Z of the other of M or M' is selected from (a), (c) or (d).~~

Claims 27-52 (Cancelled).

53. (Original) A method for identifying a dimeric tyrophostin or an analogue thereof with ability to inhibit GTPase activity of dynamin, the method comprising:
incubating the dimeric tyrophostin or analogue thereof with dynamin or a molecule having dynamin GTPase activity to provide test data; and
determining whether the dimeric tyrophostin or analogue thereof inhibits the GTPase activity of dynamin on the basis of the test data.

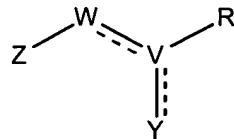
Claim 54 (Cancelled).

55. (Original) A compound of Formula III or a physiologically acceptable salt, or prodrug thereof, wherein:

M-Sp-M'

Formula III

M and M' are each independently a moiety of formula II and are the same or different, and Sp is a spacer;



Formula IV

V is C or CH ;

W is CH or a linker group; and

Y is hydrogen, cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy, sulfur, or an unsubstituted C₁-C₃ group or C₁-C₃ group substituted with at least one group independently selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur; or

W, V and Y form a 5 or 6 membered substituted or unsubstituted heterocyclic or carbocyclic ring fused with Z, wherein the heterocyclic ring includes from 1 to 3 heteroatoms selected from O, N and S, and the heterocyclic or carbocyclic ring, when substituted, has at least one substituent selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy, sulfur, or an unsubstituted C₁-C₃ group or a C₁-C₃ group substituted with at least one group independently selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur; and

R is CH₂R', CXR' or CHX'R' ;

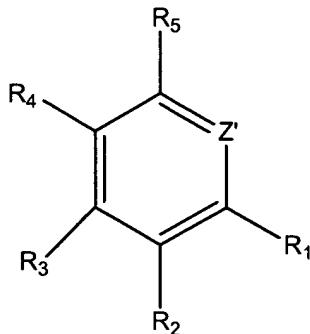
X is O or S ;

X' is cyano, nitro, amino, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy, or an unsubstituted C₁-C₃ group or C₁-C₃ group substituted with at least one group independently selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur;

R' is NH, O or S bonded to the spacer; and

Z is selected from:

- (a) an unsubstituted heterocyclic group consisting of one or two rings independently having 5 or 6 ring members including up to 3 heteroatoms selected from O, N and S;
- (b) an unsubstituted carbocyclic group consisting of one or two rings independently having 5 or 6 ring members;
- (c) a heterocyclic group consisting of one or two rings independently having 5 or 6 ring members including up to 3 heteroatoms selected from O, N and S wherein the heterocyclic group has one or more substituents independently selected from:
 - (i) nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, C₁-C₂ alkoxy and C₁-C₂ acyl ; and
 - (ii) a C₁-C₂ alkyl or C₁-C₂ alkenyl group with at least one substituent selected from nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, C₁-C₂ alkoxy and C₁-C₂ acyl ; and
- (d) a carbocyclic group consisting of one or two rings independently having 5 or 6 ring members, and at least two substituents when W is CH or a linker group or W, V and Y form an unsubstituted carbocyclic group, or at least one substituent when W, V and Y form a heterocyclic group, independently selected from:
 - (i) nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, C₁-C₂ alkoxy and C₁-C₂ acyl ; and
 - (ii) a C₁-C₂ alkyl or C₁-C₂ alkenyl group with at least one substituent selected from nitro, NH, amino, cyano, halo, hydroxy, carboxy, oxo, sulfur, sulfhydryl, C₁-C₂ alkoxy and C₁-C₂ acyl ;wherein when Z of one of M or M' is selected from (b), Z of the other of M or M' is selected from (a), (c) or (d), and with the proviso that Z of at least one of M and M' is other than a benzyl group of formula IVa when R is CXR', X is O, R' is NH bonded to the spacer, V is C, W is CH, Y is cyano, and



Formula IVa

R₁, R₂, and R₅ are H, and R₃ and R₅ are hydroxy; or

R₁ and R₅ are H, and R₂ to R₄ are hydroxy when Sp is a C₂-C₄ alkyl spacer; and
wherein Z' is a carbon atom bonded to W.

56. (Original) A compound according to claim 55 wherein:

V is C ;

W is CH ;

Y is hydrogen, cyano, nitro, amino, halo, hydroxy, sulfhydryl, carboxy,

thiocarboxy, or an unsubstituted C₁-C₂ group or C₁-C₂ group substituted with at least one group independently selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur; or

W, V and Y form a 5 or 6 membered substituted or unsubstituted heterocyclic or carbocyclic ring fused with Z, wherein the heterocyclic ring includes from 1 to 3 heteroatoms selected from O, N and S, and the carbocyclic or heterocyclic ring, when substituted, has at least one substituent selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur, or an unsubstituted C₁-C₂ group or C₁-C₂ group substituted with at least one group independently selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur; and

R is CH₂R', CXR 'or CHX'R' ;

X is O or S ; and

X' is cyano, nitro, amino, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy, or an unsubstituted C₁-C₂ group or C₁-C₂ group substituted with at least one group independently selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl ; carboxy, thiocarboxy and sulphur.

57. (Original) A compound according to claim 56 wherein:

Y is cyano, nitro, amino, carboxy, hydroxy, sulfhydryl, thiocarboxy, or a C₁-C₂ group substituted with a group selected from cyano, nitro, amino, hydroxy, sulfhydryl, carboxy and thiocarboxy;

W, V and Y form a 5 or 6 membered substituted or unsubstituted heterocyclic or carboxylic ring fused with Z, wherein the heterocyclic ring includes from 1 to 3 heteroatoms selected from O, N and S, and the carbocyclic or heterocyclic ring, when substituted, has at least one substituent selected from cyano, nitro, amino, hydroxy, sulfhydryl, carboxy and thiocarboxy, or a C₁-C₂ group substituted with a group selected from cyano, nitro, amino, hydroxy, sulfhydryl, carboxy and thiocarboxy; and

R is CXR'.

58. (Currently Amended) A compound according to any one of claims 55 to 57 wherein Z is selected from:

- (i) a heterocyclic group consisting of one or two rings independently having 5 or 6 ring members including up to 3 heteroatoms independently selected from O, N and S;
- (ii) a heterocyclic group consisting of one or two rings independently having 5 or 6 ring members including up to 3 heteroatoms independently selected from O, N and S, wherein the heterocyclic group has one or more substituents independently selected from nitro, NH, halo, cyano, amino, hydroxy, carboxy, oxo, sulfur, and C₁-C₂ alkoxy; and
- (iii) an carbocyclic group consisting of one or two rings independently having 5 or 6 ring members, and at least two substituents independently selected from nitro, NH, amino, halo, cyano, hydroxy, carboxy, oxo, sulfur and C₁-C₂ alkoxy.

59. (Currently Amended) A compound according to ~~any one of~~ claims 55 to 58 wherein Z of at least one of M and M' is other than a 2, 3-disubstituted carboxycyclic group.

60. (Currently Amended) A compound according to ~~any one of~~ claims 55 to 59 wherein Z of at least one of M and M' comprises:

at least two substituents in ortho positions relative to one another or in adjacent substitution positions, when the Z group is selected from (d) and W is CH or a C₁-C₃ linker group; or

the, or one of, the substituents on a carbon atom adjacent to the, or one of the, heteroatom (s) when the Z group is a heterocyclic group selected from (c) ; or

when W, V and Y are cyclised forming a heterocyclic ring fused with Z, the, or one of, the substituents on a carbon atom spaced at least one bond length from the heterocyclic ring.

61. (Currently Amended) A compound according to ~~any one of~~ claims 55 to 60 wherein when the Y substituent of one of M or M' is hydrogen, the Y substituent of the other of M and M' is other than hydrogen.

62. (Currently Amended) A compound according to ~~any one of~~ claims 55 to 61 wherein W, V and Y form a 5 or 6 membered heterocyclic ring fused with Z.

63. (Original) A compound according to claim 62 wherein the heterocyclic ring fused with Z forms a two ring heterocyclic group.

64. (Currently Amended) A compound according to ~~any one of~~ claims 55 to 63 wherein Z comprises an aryl group consisting of one or two rings independently having 5 or 6 ring members, and at least two substituents independently selected from nitro, NH, amino, halo, cyano, hydroxy, carboxy, oxo, sulphur and C₁-C₂ alkoxy.

65. (Original) A compound according to claim 64 wherein Z comprises an aryl group consisting of one ring having 6 ring members and at least two substituents independently selected

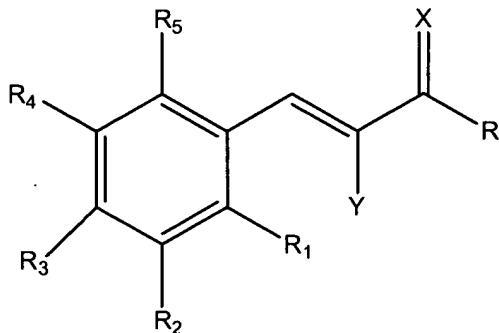
from nitro, amino, halo, cyano, hydroxy, carboxy and C₁-C₂ alkoxy.

66. (Original) A compound according to claim 65 wherein the aryl group has at least two substituents independently selected from nitro, amino, and hydroxy.

67. (Currently Amended) A compound according to ~~any one of claims 55 to 62~~ wherein Z comprises a heterocyclic group having one or two rings independently having 5 or 6 ring members including up to 3 heteroatoms selected from O, N and S, wherein the heterocyclic group has one or more substituents independently selected from nitro, NH, halo, cyano, amino, hydroxy, carboxy, oxo, sulphur and C₁-C₂ alkoxy.

68. (Original) A compound according to claim 67 wherein the heterocyclic group has one or more substituents independently selected from nitro, amino and hydroxy.

69. (Currently Amended) A compound according to ~~any one of claims 55 to 59~~ wherein M and M' are each independently a moiety as follows:



wherein: X is O or S ;

Y is cyano, nitro, amino, halo, hydroxy, sulphydryl, carboxy, or thiocarboxy; or

R₁ and Y are cyclised forming a 5 or 6 membered substituted or unsubstituted heterocyclic or carbocyclic ring, wherein the heterocyclic ring includes 1 or 2 heteroatoms selected from O, N and S, and the carbocyclic or heterocyclic ring, when

substituted, has at least one substituent selected from cyano, nitro, NH, amino, oxo, halo, hydroxy, sulfhydryl, carboxy, thiocarboxy and sulfur; and R2 to R5 are independently hydrogen or a substituent independently selected from nitro, amino, halo, hydroxy, carboxy, sulfhydryl, thiocarboxy, C₁-C₂ alkoxy and C₁-C₂ acyl ; or

R₂ to R₅ are independently hydrogen or a substituent independently selected from nitro, amino, halo, hydroxy, carboxy, sulfhydryl, thiocarboxy, halo, C₁-C₂ alkoxy and C₁-C₂ acyl ; and

R₁ to R₅ are independently hydrogen or a substituent independently selected from nitro, amino, halo, hydroxy, carboxy, sulfhydryl, thiocarboxy, halo, C₁-C₂ alkoxy and C₁-C₂ acyl ; and

R is NH, O is S bonded to the spacer Sp; and

wherein at least one of M and M' is characterised in that, at least two of R₁ to R₅, are other than hydrogen and when R₁ to R₂ are other than hydrogen at least one of R₃ to R₅ is also other than hydrogen, or when R₁ and Y are cyclised, at least two of R₂ to R₅ are other than hydrogen when R₁ and Y form an unsubstituted carbocyclic group or at least one of R₂ to R₅ is other than hydrogen when Y and R₁ form a heterocyclic group.

70. (Original) A compound according claim 69 wherein R₁ to R₃ are other than hydrogen.

71. (Original) A compound according to claim 69 wherein at least two of R₁ to R₅ are in ortho positions relative to one another.

72. (Original) A compound according to claim 69 wherein at least one of M and M' has three substituents and wherein the substituents are adjacent to one another.

73. (Original) A compound according to claim 72 wherein either R₁ to R₃ are other than hydrogen or R₂ to R₅ are other than hydrogen.

74. (Original) A compound according to claim 69 wherein when at least one of R₁ to R₅ or R₂ to R₅ is halo, C₁-C₂ alkoxy or C₁-C₂ acyl, at least one other substituent is selected from nitro, amino, hydroxy, carboxy and thiocarboxy when R₁ and Y are cyclised and form a

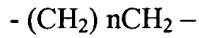
heterocyclic ring, or at least two other substituents are selected from nitro, amino, hydroxy, carboxy and thiocarboxy when R₁ and Y are not cyclised or form an unsubstituted carboxylic ring.

75. (Currently Amended) A compound according to ~~any one of~~ claims 69 to 74 wherein Y is cyano, X is O and R is NH.

76. (Currently Amended) A compound according to ~~any one of~~ claims 55 to 75 wherein M and M' are the same.

77. (Currently Amended) A compound according to ~~any one of~~ claims 55 to 76 wherein the spacer Sp permits the compound to adopt a hairpin conformation.

78. (Currently Amended) A compound according to ~~any one of~~ claims 55 to 77 wherein the spacer Sp comprises an unsubstituted alkane chain as follows:



wherein n is an integer of from 1 to 5.

79. (Currently Amended) A compound according to ~~any one of~~ claims 1 to 78 wherein the compound of Formula I is a dimeric tyrphostin.

80. (Currently Amended) A pharmaceutical composition comprising a compound as defined in ~~any one of~~ claims 55 to 58 together with a physiologically acceptable excipient, carrier or diluent. remarks